

19



Europäisches Patentamt
European Patent Office
Office européen des brevets

Search in the European Search
Report of EP02 79 5857.8
Your Ref.: 01-40326-EP(848366.20220)

11

Publication number:

**0 020 794
A1**

12

EUROPEAN PATENT APPLICATION

21

Application number: **79101829.4**

51

Int. Cl.³: **A 61 K 9/10**

22

Date of filing: **08.06.79**

43

Date of publication of application: **07.01.81**
Bulletin 81/1

71

Applicant: **Toko Yakuhin Kogyo Kabushiki Kaisha,**
No 12-23, Honjonishi 2-chome, Ooyodo-ku Osaka-shi,
Osaka-fu (JP)

72

Inventor: **Kamishita, Takuzo, No 12-28,**
Tonda-cho 6-chome, Takatsuki-shi Osaka-fu (JP)
Inventor: **Kamishita, Kazuhiko, No 12-27,**
Tonda-cho 6-chome, Takatsuki-shi Osaka-fu (JP)

84

Designated Contracting States: **DE FR GB IT**

74

Representative: **von Kreisler, Alek, Dipl.-Chem. et al,**
Deichmannhaus am Hauptbahnhof, D-5000 Köln 1 (DE)

54

Creamy preparation containing steroid and process for the preparation thereof.

57

A creamy preparation containing a steroid compound having a pH of 4 to 7 and a viscosity of 10 000 to 1000 000 centipoises, which is applicable to the skin and comprises a steroid compound (corticosteroids), a fluid oily substance, a nonionic surfactant, and an aqueous solution of carboxyvinyl polymer, said preparation having been neutralized with a basic substance, and a process for the preparation thereof. The creamy preparation has an excellent absorbability of the active steroid, excellent stability and excellent spreadability onto the skin and also good feeling in use.

EP 0 020 794 A1

ACTORUM AG

CREAMY PREPARATION CONTAINING STEROID AND
PROCESS FOR THE PREPARATION THEREOF

The present invention relates to a novel creamy preparation containing a steroid compound which is applicable to skin. More particularly, it relates to a creamy preparation having a pH of 4 to 7 and a
5 viscosity of 10,000 to 100,000 centipoises at 20°C which is prepared by dissolving a steroid compound in crotamiton and/or propylene glycol, adding to the solution a fluid oily substance, a nonionic surfactant and an aqueous solution of a carboxyvinyl polymer, and add-
10 ing with stirring thereto a water-soluble basic substance.

It is well known that some steroid compounds such as prednisolone, dexamethasone, cortisone, etc. have excellent antiinflammatory activities and are
15 usually used as an antiinflammatory agent in the form of an ointment. However, ointments feel sticky and unpleasant when applied to the skin, and further, due to insufficient contact of the steroid with the skin, the steroid is insufficiently absorbed from the skin.
20 Moreover, the applied surface is rubbed with clothes, which results in loss of the active ingredient and also soiling of clothes. Besides, at a high temperature of 40°C or higher, ointments are liable to become unstable.

In order to overcome the drawbacks of ointment, the present inventors have provided a transparent, gelatinous preparation which is prepared by mixing a solution of a steroid compound in crotamiton with propylene glycol and adding the resulting mixture to an aqueous solution of a carboxyvinyl polymer and finally adding an organic amine to the resulting mixture (cf. U.S. Patent 4,008,321).

As a result of a further studying by the present inventors, there has been found a creamy preparation of a steroid compound which has greater stability and excellent feeling in use.

The present invention provides a novel creamy preparation of a steroid compound having a pH of 4 to 7 and a viscosity of 10,000 to 100,000 centipoises at 20°C, which is prepared by dissolving a steroid compound in crotamiton and/or propylen glycol, adding thereto a fluid oily substance, a nonionic surfactant and an aqueous solution of a carboxyvinyl polymer, and adding with stirring thereto a water-soluble basic substance while heating the mixture at about 70 to 80°C.

The steroids to be contained in the present creamy preparation include corticosteroids and esters thereof, such as prednisolone, cortisone, triamcinolone, bethamethasone, hydrocortisone, dexamithasone, methylprednisolone, fluocinolone, fluorometholone, triamcinolone acetonide, fluocinolone acetonide, fluo-

cinonide, clobetasol 17-propionate, dexamethasone valerate, betamethasone valerate, betamethasone acetate, betamethasone benzoate, flumethasone, prednisolone acetate, hydrocortisone valerate, dexamethasone valerate, 5 betamethasone propionate, betachlomethasone dipropionate, or the like. The steroid compounds are incorporated into the present creamy preparation in an effective amount which varies depending on the kinds of the steroids, but is usually in a range of 0.001 to 1 % 10 by weight based on the total weight of the preparation.

These steroids are usually insoluble in water, but are easily soluble in crotamiton (i.e. N-crotonyl-N-ethyl-o-toluidine). In the present invention, the steroids are firstly dissolved in crotamiton or propylene 15 mglycol or a mixture thereof. The steroids are dissolved ore in crotamiton than in propylene glycol. Although crotamiton can be used alone, it is not preferable to include the crotamiton of 10 % by weight or more in the present creamy preparation. Besides, propylene glycol 20 may also be used alone, but because of less solubility of steroids in propylene glycol, it is usually used only when the steroid compound has a comparatively high solubility in propylene glycol, for instance, in case of dexamethasone.

25 Accordingly, it is preferable to use a mixture of crotamiton and propylene glycol. Dissolution of a steroid compound in a mixture of crotamiton and

propylene glycol may be carried out by firstly dissolving the steroid compound in either one of crotamiton and propylene glycol and adding another one to the solution. To use the mixture of crotamiton and propylene glycol is preferable also from the viewpoint that it can give an excellent emulsion stability and spreadability to the preparation. When propylene glycol is used in a too large amount, the preparation has undesirable irritation to the skin, and hence, it should be used in an amount of less than 20 % by weight. From the standpoint of solubility of steroids in the solvent, prevention of crystallization of steroids in the preparation, and further emulsion stability, spreadability and feeling of the preparation, crotamiton is usually used in an amount of not more than 10 % by weight, usually 0.5 to 10 % by weight, preferably 2 to 10 % by weight, and propylene glycol is usually used in an amount of less than 20 % by weight, i.e. from 2 to less than 20 % by weight, preferably 5 to 10 % by weight, based upon the total weight of the preparation.

Fluid oily substance to be incorporated into the present creamy preparation includes higher fatty alcohols, higher fatty acids and higher fatty acid esters, oily hydrocarbons, and a mixture thereof. Suitable examples of the fluid oily substance are fatty alcohols having 8 to 18 carbon atoms, such as octyl alcohol, capryl alcohol, nonyl alcohol, lauryl alcohol, myristyl alcohol, cetyl alcohol, or stearyl alcohol; monovalent or divalent

fatty acids having 8 to 18 carbon atoms, such as lauric acid, myristic acid, palmitic acid, oleic acid, linoleic acid, sebacic acid, or stearic acid; alkyl esters of the fatty acids as mentioned above wherein the alkyl moiety
5 has 1 to 18 carbon atoms, such as isopropyl myristate, diethyl sebacate, dibutyl sebacate, dioctyl sebacate, and a mixture thereof.

The carboxyvinyl polymer is a hydrophilic vinyl polymer with active carboxyl groups which is prepared by
10 polymerization of monomers comprising predominantly acrylic acid [cf. Chem. & Eng. News, Vol. 36, page 64 (Sept. 29, 1958)]. All commercially available carboxyvinyl polymers can be used in the present invention. Suitable examples are Carbopol 934, Carbopol 940 and
15 Carbopol 941, which are tradenames of the products of Goodrich Chemical. The carboxyvinyl polymer has free carboxyl groups and the aqueous solution is acidic. When the carboxyvinyl polymer is neutralized with a basic substance, a sticky gel is formed.

20 The basic substance to be used for neutralization of carboxyvinyl polymer includes organic amines, such as an alkylamine having 1 to 4 carbon atoms (e.g. methylamine, ethylamine, or propylamine), a dialkylamine having 1 to 4 carbon atoms in each alkyl moiety (e.g.
25 dimethylamine, diethylamine, or dipropylamine), a trialkylamine having 1 to 4 carbon atoms in each alkyl moiety (e.g. trimethylamine, triethylamine, or tripropyl-

amine), an alkanolamine having 1 to 4 carbon atoms in the alkanol moiety (e.g. methanolamine, ethanolamine, or propanolamine), a dialkanolamine having 1 to 4 carbon atoms in each alkanol moiety (e.g. dimethanolamine, di-
5 ethanolamine, dipropanolamine, or dibutanolamine), a tri-
alkanolamine having 1 to 4 carbon atoms in each alkanol moiety (e.g. trimethanolamine, triethanolamine, tri-
propanolamine, or tributanolamine), and trimethylolamino-
methane, and also includes inorganic bases such as
10 ammonia, an aqueous solution of alkali metal hydroxides (e.g. sodium hydroxide, or potassium hydroxide). All these basic substances can give a gel having a similar viscosity when the aqueous solution of carboxyvinyl polymer is neutralized with the basic substances.

15 The nonionic surfactant to be incorporated into the present creamy preparation includes sorbitan sesquioleate, sorbitan trioleate, sorbitan monooleate, sorbitan monostearate, sorbitan monolaurate, polyethylene glycol monostearate, polyoxyethylene sorbitan mono-
20 oleate, polyoxyethylene sorbitan monolaurate, polyoxyethylene nonylphenyl ether, polyoxyethylene cetyl ether, polyoxyethylene lauryl ether, or a mixture thereof.

The creamy preparation of the present invention can be prepared in the following manner.

25 A steroid compound is firstly dissolved in crotamiton or polyethylene glycol or a mixture thereof (mixed ratio of crotamiton : polyethylene glycol, 1 : 10

to 5 : 1 by weight). To the solution are added a fluid oily substance, a nonionic surfactant and an aqueous solution of carboxyvinyl polymer, and thereto is added with stirring a water-soluble basic substance, by which the carboxyvinyl polymer is neutralized to give a viscous gel. The above step, i.e. the dissolution of the steroid compound in the solvent and the mixing the ingredients may be carried out at room temperature but are preferably carried out at about 70 to 80°C.

According to the action of the nonionic surfactant, the oily phase of the mixture of a steroid compound and a fluid oily substance and the aqueous phase of the carboxyvinyl polymer solution are uniformly mixed to give the desired creamy preparation. The creamy preparation thus obtained has a pH of 4 to 7, preferably 4 to 5.5 and a viscosity of 10,000 to 100,000 centipoises, preferably 30,000 to 80,000 centipoises, at 20°C. The creamy preparation contains 0.1 to 3.0 % by weight, preferably 0.5 to 1.2 % by weight, of the carboxyvinyl polymer based upon the total weight of the preparation. The carboxyvinyl polymer is usually used in the form of a 1 to 10 % aqueous solution, preferably 2 to 4 % aqueous solution, and after mixing the aqueous solution of carboxyvinyl polymer with the mixture of a steroid compound and other ingredients, the content of the carboxyvinyl polymer in the creamy preparation is regulated in the above range by adding thereto water.

The pH of the preparation is regulated within 4 to 7 by controlling the amount of the basic substance. When the pH value is higher than 7, i.e. in alkaline side, the preparation is unstable, and on the other hand, 5 it is lower than 4, the preparation becomes too acidic and irritative to skin and further too large amount of carboxycinyl polymer is undesirably required for increasing the viscosity thereof.

The fluid oily substance is usually used in 10 an amount of 5 to 50 % by weight, preferably 10 to 20 % by weight, based upon the total weight of the preparation, but when crotamiton, which is also an oily substance, is used in a large amount, the fluid oily substance is used in a less amount. The nonionic surfactant 15 is used in an amount of 0.5 to 5 % by weight, preferably 1 to 2 % by weight, based upon the total weight of the preparation..

The creamy preparation of the present invention is a uniform white cream and the viscosity thereof 20 does almost not vary at a high temperature (e.g. 40°C) and at a low temperature (e.g. 0°C) and also even when the preparation is kept for a long period of time. Moreover, even when the preparation is kept at a low temperature for a long period of time, no crystalliza- 25 tion of the steroid compound appears. Accordingly, the present creamy preparation is very stable and does not have such drawbacks as seen in the conventional ointments, such as melting or liquefaction at summer time and hard-

ening or solidification at winter time and also separation of the oily phase and aqueous phase.

When the creamy preparation of the present invention is applied to skin, it is contacted with salts
5 such as sodium chloride which are contained in a very small amount in the perspiration or are present on the surface of the skin and thereby the viscoisty of the preparation is rapidly decreased, and the preparation is liquefied and shows excellent spreadability onto
10 the skin. As the result, a film of carboxyvinyl polymer is formed on the skin, which promotes the absorption of the active ingredient (steroid compound) into skin. Moreover, the film of carboxyvinyl polymer thus formed is readily dried when contacted with air, and hence, the
15 skin surface, to which the preparation is applied, is not sticky and is smooth. Thus, the drawbacks of ointments, such as soiling of clothes and bad feeling, can be eliminated.

The creamy preparation of the present invention
20 may optionally be incorporated with other active ingredients such as antihistaminics, analgesics, or the like.

The creamy preparation of the present invention and method for the preparation thereof are illustrated by the following Examples, but the present invention is not
25 limited thereto. In the Examples, the purified water was prepared by purifying water with an ion exchange resin, and the viscosity was measured at 20°C by a C-type viscosimeter (made by Tokyo Keiki Co., Ltd. Japan).

Example 1

Dexamethasone acetate (25 mg) was dissolved in crotamiton (5 g) at about 70°C, and thereto were added isopropyl myristate (10 g), propylene glycol (10 g), polyoxyethylene sorbitan monolaurate (1 g), a 4 % aqueous solution of a carboxyvinyl polymer (17 g), purified water (53 g) and a 1 % aqueous solution of disodium edetate (1.2 g). The mixture was heated until about 70 to 80°C on a water bath and thereto was added with stirring a 2 % aqueous sodium hydroxide solution (2 g), and further, purified water was added thereto until the total amount became 100 g. The mixture was well stirred and then cooled to give a creamy preparation having a viscosity of 60,000 centipoises and a pH of 4.30.

Example 2

Fluocinonide (50 mg) was dissolved in crotamiton (7 g) with warming, and thereto were added liquid paraffin (10 g), propylene glycol (10 g), polyoxyethylene lauryl ether (1 g), a 4 % aqueous solution of carboxyvinyl polymer (20 g), purified water (47 g) and a 1 % aqueous solution of disodium edetate (1.2 g). The mixture was heated until about 70 to 80°C on a water bath, and thereto was added with stirring a 2 % aqueous solution of triethanolamine (4.68 g), and further purified water added thereto until the total amount became 100 g. The mixture was stirred well and then

cooled to give a creamy preparation having a viscosity of 65,000 centipoises and a pH of 4.47.

Example 3

Prednisolone (500 mg) was dissolved in cro-
5 tamiton (10 g) with warming, and thereto were added iso-
propyl myristate (10 g), propylene glycol (10 g), poly-
oxyethylene sorbitan monostearate (1.5 g), a 4 % aqueous
solution of carboxyvinyl polymer (17 g), purified water
(48 g) and a 1 % aqueous solution of disodium edetate
10 (1.2 g). The mixture was heated until about 70 to 80°C
on a water bath and thereto was added with stirring a
2 % aqueous solution of triethylamine 2.95 g), and fur-
ther, purified water was added thereto until the total
amount became 100 g. The mixture was stirred well and
15 then cooled to give a creamy preparation having a vis-
cosity of 54,000 centipoises and a pH of 4.65.

Example 4

Dexamethasone (25 mg) was dissolved in propyl-
ene glycol (20 g) with warming, and thereto were added
20 isopropyl myristate (10 g), polyoxyethylene sorbitan
(1.0 g), a 4 % aqueous solution of carboxyvinyl polymer
(13 g), purified water (57 g) and a 1 % aqueous solu-
tion of disodium edetate (1.2 g). The mixture was
heated until about 70 to 80°C on a water bath and there-
25 to was added with stirring a 2 % aqueous solution of
triethanolamine (5.2 g), and further, purified water was
added thereto until the total amount became 100 g.

The mixture was stirred well and then cooled to give a creamy preparation having a viscosity of 43,000 centipoises and a pH of 4.80.

Example 5

5 Hydrocortisone (500 mg) was dissolved in cro-
tamiton (5 g) with warming, and thereto were added
liquid paraffin (10 g), propylene glycol (10 g), poly-
oxyethylene lauryl ether (1.5 g), a 4 % aqueous solu-
tion of carboxyvinyl polymer (27 g), purified water
10 (38 g) and a 1 % aqueous solution of disodium edetate
(1.2 g). The mixture was heated until about 70 to 80°C
on a water bath, and thereto was added with stirring a
2 % aqueous sodium hydroxide solution (10 g), and fur-
ther purified water added thereto until the total amount
15 became 100 g. The mixture was stirred well and then
cooled to give a creamy preparation having a viscosity
of 35,000 centipoises and a pH of 5.30.

Example 6

 Triamcinolone acetonide (100 mg) was dissolved
20 in crotamiton (7 g) with warming, and thereto were added
isopropyl myristate (10 g), propylene glycol (10 g),
polyoxyethylene sorbitan monolaurate (1 g), a 4 % aque-
ous solution of carboxyvinyl polymer (22 g), purified
water (41 g) and a 1 % aqueous solution of disodium
25 edetate (1.2 g). The mixture was heated until about 70
to 80°C on a water bath and thereto was added with stir-
ring a 2 % aqueous solution of triethylamine (6.5 g),

and further, purified water was added thereto until the total amount became 100 g. The mixture was stirred well and then cooled to give a creamy preparation having a viscosity of 75,000 centipoises and a pH of 4.53.

What is claimed is:

1. A creamy preparation which comprises a steroid compound, a solvent selected from crotamiton, propylene glycol and a mixture thereof, a fluid oily substance, a nonionic surfactant, and an aqueous solution of carboxyvinyl polymer, said preparation having been neutralized with a basic substance and having a pH of 4 to 7 and a viscosity of 10,000 to 100,000 centipoises at 20°C, and containing said fluid oily substance in an amount of 5 to 50 % by weight, said nonionic surfactant in an amount of 0.5 to 5 % by weight, and carboxyvinyl polymer in an amount of 0.1 to 3.0 % by weight, based upon the total weight of the preparation.

2. A creamy preparation according to claim 1, wherein the solvent is a mixture of crotamiton and propylene glycol, and said preparation containing crotamiton in an amount of 2 to 10 % by weight and propylene glycol in an amount of 2 to less than 20 % by weight based upon the total weight of the preparation.

3. A creamy preparation according to claim 1, wherein the steroid compound is contained in an amount of 0.001 to 1 % by weight based upon the total weight of the preparation.

4. A process for the preparation of a creamy preparation of a steroid compound, which comprises dissolving a steroid compound in a solvent selected from the group consisting of crotamiton, propylene glycol and

a mixture thereof, adding thereto a fluid oily substance, a nonionic surfactant, a 1 to 10 % aqueous solution of carboxyvinyl polymer, and then neutralizing the mixture with a basic substance to give a creamy preparation having a pH of 4 to 7 and a viscosity of 10,000 to 100,000 centipoises and containing said fluid oily substance in an amount of 5 to 50 % by weight, said nonionic surfactant in an amount of 0.5 to 5 % by weight, and carboxyvinyl polymer in an amount of 0.1 to 3.0 % by weight, based upon the total weight of the preparation.

5. A process according to claim 4, wherein the solvent is a mixture of crotamiton of 2 to 10 % by weight and propylene glycol of 2 to less than 20 % by weight, based upon the total weight of the preparation.



European Patent
Office

EUROPEAN SEARCH REPORT

0020794
Application number
EP 79 10 1829

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	<u>FR - M - 0 001 443</u> (J.R. GEIGY) * Abstract; page 1, column 1, paragraph 1 - page 2, column 1, paragraph 1; examples 1,2 *	1	A 61 K 9/10
	--		
A	<u>FR - A - 2 116 444</u> (I.C.I.) * Claims; page 2, line 24 - page 4, line 34; examples *	1	
	--		
A	<u>FR - A - 2 207 692</u> (E.R. SQUIBB & SONS) * Claims; page 1, line 1 - page 3, line 22; examples *	1	TECHNICAL FIELDS SEARCHED (Int.Cl. ³) A 61 K 9/10 9/08 9/06
	--		
A,D	<u>US - A - 4 008 321</u> (T. KAMISHITA) * Abstract; claims *	1	
	--		
A	<u>DE - A - 2 207 294</u> (WARNER-LAMBERT) * Claims; examples *	1	
	--		
A	<u>DE - A - 2 309 448</u> (SYNTEX) * Claims; page 3, paragraph 3 - page 10, paragraph 1; examples *	1	CATEGORY OF CITED DOCUMENTS X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
	--		
A	<u>DE - A - 2 306 311</u> (SYNTEX) * Claims; page 2, last paragraph - page 7, paragraph 2; page 9, paragraph 2 - page 10, paragraph 1; examples *	1	

<input checked="" type="checkbox"/> The present search report has been drawn up for all claims			&: member of the same patent family, corresponding document
Place of search The Hague		Date of completion of the search 30-01-1980	Examiner VANHECKE

EPO Form 1503.1 08.78

THIS PAGE BLANK (USE FOR)